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# Association of Dysregulated Central Pain Processing and Response to Disease-Modifying Antirheumatic Drug Therapy in Rheumatoid Arthritis

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**Objective.** To determine the association between dysregulated central pain processing and treatment response in rheumatoid arthritis (RA).

**Methods.** One hundred eighty-two participants with active RA were followed up for 12 weeks after starting a disease-modifying antirheumatic drug (DMARD). To assess central pain processing, participants underwent quantitative sensory testing (QST), including assessment of pressure pain thresholds (PPTs) at the trapezius muscles, temporal summation, and conditioned pain modulation (CPM). QST measures were categorized as high central dysregulation versus low central dysregulation. The association between baseline central dysregulation and treatment response, as defined by the European League Against Rheumatism (EULAR) response criteria, was assessed using multiple logistic regression adjusted for demographic characteristics, RA-related variables, and psychosocial variables.

**Results.** A good EULAR response was achieved in fewer participants with high CPM dysregulation than participants with low CPM dysregulation (22.5% versus 40.3%; $P = 0.01$). A similar trend, though not significant, was noted when central dysregulation was assessed with PPT and temporal summation. The adjusted odds ratios (ORs) for the association between high central dysregulation and good EULAR response were 0.59 for PPTs (95% confidence interval [95% CI] 0.28–1.23), 0.60 for temporal summation (95% CI 0.27–1.34), and 0.40 for CPM (95% CI 0.19–0.83). In a model examining the combined effects of dysregulated temporal summation and CPM, dysregulation of both measures was associated with lower odds of achieving a good EULAR response (OR 0.23 [95% CI 0.07–0.73]).

**Conclusion.** Low CPM was significantly associated with lower odds of achieving a good EULAR response, suggesting that inefficient descending inhibitory mechanisms may be a potential treatment target for further study.

## INTRODUCTION

Despite the availability of potent disease-modifying antirheumatic drugs (DMARDs), less than half of patients with rheumatoid arthritis (RA) achieve low disease activity, measured by composite disease activity indices, after 6 months of therapy (1). While composite disease activity measures, such as the Disease Activity Score in 28 joints (DAS28) (2), are considered surrogates of peripheral joint inflammation, they include subjective components such as the tender joint count (TJC) and patient global assessment of disease activity (PtGA), which may be influenced by non-inflammatory factors. Our group and others have shown that TJC and PtGA are associated with dysregulated central pain processing, termed pain centralization (3,4).

Pain centralization is characterized by widespread pain due to increased responsiveness of central nervous system (CNS)

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nociceptive neurons to normal or subthreshold afferent input (5). Pain centralization has been assessed using quantitative sensory testing (QST) in a variety of musculoskeletal conditions, including fibromyalgia, osteoarthritis (OA), and RA (6). The most commonly used QST modality is the assessment of pressure pain thresholds (PPTs), which detect overall sensitivity to pressure. Low PPTs at extraarticular sites (e.g., trapezius muscles) are thought to reflect abnormalities in central pain processing (7). Specific abnormalities in central pain processing may be detected by increased temporal summation, which is associated with enhanced facilitation of pain, and decreased conditioned pain modulation (CPM), which is associated with diminished inhibition of pain (8,9).

Several studies have noted QST abnormalities in patients with RA. For instance, patients with RA have lower PPTs than healthy controls, reflecting higher pain sensitivity (10,11). Additional studies have reported facilitated temporal summation and inefficient CPM in RA patients compared to healthy controls (11,12). However, those studies were cross-sectional, and the longitudinal relationship between pain centralization and response to therapy in RA is largely unknown. The objective of this study was to assess baseline pain centralization as a predictor of a good European League Against Rheumatism (EULAR) response to DMARD therapy in a prospective, longitudinal cohort of patients with active RA. We hypothesized that participants with high central dysregulation at baseline would have lower odds of achieving good EULAR response.

## PATIENTS AND METHODS

**Study population.** This study is a longitudinal analysis of participants from the Central Pain in Rheumatoid Arthritis (CPIRA) cohort. CPIRA is a multicenter, prospective, observational study of participants with active RA necessitating DMARD initiation or change (13). Participants were recruited from 5 US academic medical centers from January 2014 to July 2017. Inclusion criteria were diagnosis of RA based on the American College of Rheumatology (ACR)/EULAR 2010 criteria (14) and starting or switching a DMARD due to active RA. Exclusion criteria were: 1) use of centrally acting pain medications (e.g., amitriptyline, gabapentin, or duloxetine) within 3 months of enrollment; 2) receiving >10 mg of prednisone or its equivalent; 3) chronic opioid use or any opioid use within 24 hours of the study start date; 4) systemic autoimmune disease other than RA; 5) severe Raynaud's disease requiring pharmacologic treatment; 6) severe peripheral vascular disease manifested by claudication or ischemic rest pain; and 7) peripheral neuropathy. Participants were ineligible for this longitudinal analysis if they: 1) failed to start a DMARD within 1 month of the baseline visit; 2) stopped taking the new DMARD within 6 weeks of initiation; 3) had no follow-up visit to assess outcome measures; or 4) were missing baseline covariates or QST measurements. The choice of DMARD was left to the discretion of the physician, as we assumed that the effect of DMARDs on dysregulated pain processing would be equivalent across DMARDs.

**Quantitative sensory testing.** All participants underwent QST prior to DMARD initiation or change and ~3 months after starting the new DMARD, as described previously (3). Briefly, all assessors underwent a 1-day training session on the use of QST. Assessments of interrater reliability were performed. We calculated a two-way mixed single score intraclass correlation coefficient (ICC [3,1]) to assess reproducibility of QST between assessors (15). ICCs ranged from 0.71 to 0.90 for the PPT and temporal summation measures. The ICC for CPM was 0.45. Per Cicchetti, ICCs of 0.40–0.59 are fair, 0.60–0.74 are good, and 0.75–1.00 are excellent (16).

*PPTs.* A Wagner Force Ten FDX algometer was used to assess PPTs at the bilateral trapezius muscles. The algometer probe was placed on the center of the trapezius muscle, and force was applied at 0.5 kgf/second until pain was reported. Three trials were performed per side. The PPT was defined as the mean pressure at which pain was reported. The trapezius muscle was chosen as the site for assessment of PPTs for the following reasons: 1) the trapezius muscle is a commonly used site for PPTs in the pain literature allowing for comparisons to other studies; 2) normal values for PPTs have been reported at the trapezius muscle; and 3) the trapezius muscle is distant from joints commonly affected by RA, minimizing confounding effects of peripheral sensitization from active joint inflammation (17,18). Low PPTs were considered indicative of pain centralization.

*Temporal summation.* Participants were tested using 6 flat-tipped probes, with weights ranging from 8 mN to 256 mN. Probes of increasing weight were tested on the participant's dorsal forearm until a pain score of 30–40 of a possible maximum of 100 was produced. The probe generating a pain score between 30 and 40 was used for further testing; if no such pain rating was achieved, then the highest weighted probe was used. The selected probe was tapped 10 times on the dorsal forearm for 0.5 seconds per tap. The participant was asked to rate his/her pain on a scale of 0–100 at taps 1, 5, and 10. Temporal summation was calculated by subtracting the pain score at the first tap from the pain score at the 10th tap. The mean temporal summation was calculated by taking the average of 3 trials. The resulting value was divided by 10 to normalize to a standardized 0–10 pain scale. Higher temporal summation values were indicative of higher levels of pain centralization.

*CPM.* CPM was assessed using a painful conditioning stimulus to activate the descending inhibitory pain pathways and a test stimulus to assess pain sensitivity. The conditioning stimulus was produced by inserting the participant's right hand into a 5–7°C water bath. The test stimulus was pressure produced by an algometer placed at the center of the contralateral trapezius. PPTs were measured immediately prior to hand submersion in the cold-water bath and after 20 seconds of cold-water

submersion. The ratio of the first PPT to the second PPT was calculated. Inefficient (lower) CPM was considered indicative of pain centralization.

**Assessment of clinical variables.** Baseline clinical variables were assessed at the initial study visit prior to DMARD initiation or change. These variables included age, sex, race, body mass index (BMI), education level, and RA disease duration. Comorbidity was assessed via a modified version of the Charlson comorbidity score (19). Symptoms of depression and sleep disturbance were assessed by the Patient-Reported Outcomes Measurement Information System (PROMIS) computerized assessment tests. Serum from the baseline visit was analyzed for C-reactive protein level (CRP), rheumatoid factor (RF), and anti–cyclic citrullinated peptide antibody (anti-CCP) at a single laboratory. Serum for CRP measurement was additionally obtained at the 12-week visit. PtGA, tender joint count in 28 joints (TJC28), and swollen joint count in 28 joints (SJC28) were obtained by a trained assessor at the initial study visit and at the 12-week study visit following DMARD initiation or change. The DAS28 using the C-reactive protein level (DAS28-CRP) was calculated as previously described (20).

**Statistical analysis.** The primary outcome measure was good response, as defined by the EULAR response criteria, at the 12-week visit (21). A good EULAR response was defined as a DAS28-CRP of ≤3.2 at the 12-week follow-up visit and a change in DAS28-CRP from baseline of >1.2.

The primary predictors were PPTs at the trapezius muscle, temporal summation, and CPM. To avoid assumptions of linearity and to address differences in pain sensitivity between men and women, the QST measures were categorized into sex-specific tertiles (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41440/abstract). For ease of interpretation, each QST measure was further grouped into a low dysregulation group (defined as the least centrally dysregulated tertile) and a high dysregulation group (defined as the middle and most centrally dysregulated tertiles). For PPTs and CPM, the low dysregulation group was tertile 3 (highest values of PPTs and CPM), and the high dysregulation group included both tertiles 1 and 2 (lower values of PPTs and CPM). For temporal summation, the low dysregulation group was tertile 1 (lowest values of temporal summation), and the high dysregulation group included both tertiles 2 and 3 (higher values of temporal summation) (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.41440/abstract). We chose this cut point because participants with temporal summation in the 2nd and 3rd tertiles reported greater pain severity than participants with temporal summation in the 1st tertile in a previous study (13). Similar results were found for PPTs. For consistency, we chose this categorization strategy for all QST modalities, including CPM, in the present study.

The secondary predictor was a combined measure of temporal summation and CPM. The purpose of the secondary analysis was to assess how different combinations of altered central mechanisms of pain processing would affect DMARD response. We grouped participants into 4 combinations: 1) low temporal summation and low CPM dysregulation (referent group); 2) predominantly temporal summation dysregulation (high temporal summation and low CPM dysregulation); 3) predominantly CPM dysregulation (low temporal summation and high CPM dysregulation; and 4) high temporal summation and high CPM dysregulation. These combinations were chosen a priori. We chose to include only temporal summation and CPM in these analyses, as they are considered measures of specific pain-processing mechanisms. Temporal summation is considered primarily a measure of spinal facilitation of pain, and CPM is considered primarily a measure of descending pain modulation (22–24). We did not include PPTs in the secondary analysis, as PPTs are general measures of hyperalgesia, which do not imply specific mechanisms of dysregulated pain processing; rather, altered PPTs could be the result of both peripheral and central mechanisms.

The percentage of participants achieving a good EULAR response in each group was calculated. Associations between baseline QST measures and a good EULAR response were examined using multiple logistic regression. All adjusted models included age, sex, race, and education level. In addition, BMI, PROMIS depression, and PROMIS sleep disturbance were included as covariates due to previously reported associations with pain (12,25). Seropositivity (defined as the presence of either RF of ≥14 IU/ml or anti-CCP ≥17 units/ml), RA disease duration, and the modified Charlson comorbidity score were also included in the models based on clinical experience suggesting possible relationships with pain. A site variable was used to account for potential population differences among study sites.

Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between high central dysregulation and good EULAR response were calculated. Unadjusted and adjusted ORs were additionally calculated for the combined measure of temporal summation and CPM, with the low temporal summation and low CPM group as referent. Trend tests were conducted to evaluate the linear trend in the degree of central dysregulation defined by the combined measure of temporal summation and CPM. For the trend test analysis, we hypothesized that the odds of achieving good EULAR response would decrease with the increasing number of dysregulated mechanisms. We ranked temporal summation below CPM because it has been suggested that enhanced spinal facilitation of pain signaling, measured by temporal summation, may be reversible upon resolution of peripheral noxious input (e.g., joint inflammation in RA) (26). In contrast, altered baseline descending inhibition of pain is not thought to be reversible. To explore the relationship between central pain dysregulation and specific components of treatment response, a post hoc analysis was performed comparing mean

**Table 1.** Clinical characteristics of the participants with complete data (n = 182)*

| | |
|---|---|
| Age, years | 55.2 ± 14.4 |
| Female, % | 83.0 |
| White, % | 76.9 |
| BMI, kg/m$^2$ | 28.5 ± 7 .0 |
| Some college or higher, % | 75.3 |
| Seropositive, % | 70.3 |
| RA disease duration, years | 10.1 ± 12.5 |
| PROMIS depression† | 50.3 ± 9.2 |
| PROMIS sleep disturbance† | 54.7 ± 8.9 |
| Charlson comorbidity score | 1.3 ± 1.0 |
| DAS28-CRP | 4.3 ± 1.3 |
| PtGA | 4.2 ± 2.4 |
| TJC28 | 10.9 ± 8.6 |
| SJC28 | 5.3 ± 5.3 |
| CRP, mg/liter | 7.7 ± 12.2 |

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; RA = rheumatoid arthritis; PROMIS = Patient-Reported Outcomes Measurement Information System; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; PtGA = patient global assessment of disease activity; TJC28 = tender joint count in 28 joints; SJC28 = swollen joint count in 28 joints.
† Reported as T score.

changes in TJC, SJC, PtGA, and CRP levels between participants with high CPM dysregulation and those with low CPM dysregulation. Statistical testing used a nominal α = 0.05. All analyses were performed using SAS software version 9.4.

## RESULTS

Two hundred thirty-seven participants were eligible for the longitudinal analysis. Of these, 55 participants were excluded from the final analysis due to missing data in the primary outcome measure or baseline variables. Participants excluded for missing data had similar baseline characteristics compared to those included in the cohort (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41440/abstract).

The final analysis included 182 participants with complete data (Table 1). The mean age was 55.2 years, and 83.0% of the participants were female. The mean RA disease duration was 10.1 years, and the mean DAS28-CRP was 4.3. After 12 weeks, a good EULAR response was achieved in 28.6% of the participants while a moderate EULAR response was achieved in 32.4%, and no EULAR response was achieved in 39.0% of the participants.

A good EULAR response was achieved in fewer participants with high CPM dysregulation compared to participants with low CPM dysregulation (22.5% versus 40.3%; $P = 0.01$) (Figure 1). A similar trend was observed when high central dysregulation was assessed via PPTs or temporal summation, but statistical significance was not reached (for PPTs, 24.6% versus 36.7%; $P = 0.09$, and for temporal summation, 26.2% versus 34.6%; $P = 0.25$). The adjusted OR for achieving good EULAR response was statistically significant in participants with high CPM dysregulation compared to those with low CPM dysregulation (OR 0.40 [95% CI 0.19–0.83]) (Table 2). The same trends were seen for PPTs and temporal summation but were not statistically significant (for PPTs, OR 0.59 [95% CI 0.28–1.23]; for temporal summation, OR 0.60 [95% CI 0.27–1.34]). To better understand which components drove the association between CPM and EULAR response, we calculated mean 12-week changes in the DAS28-CRP components in

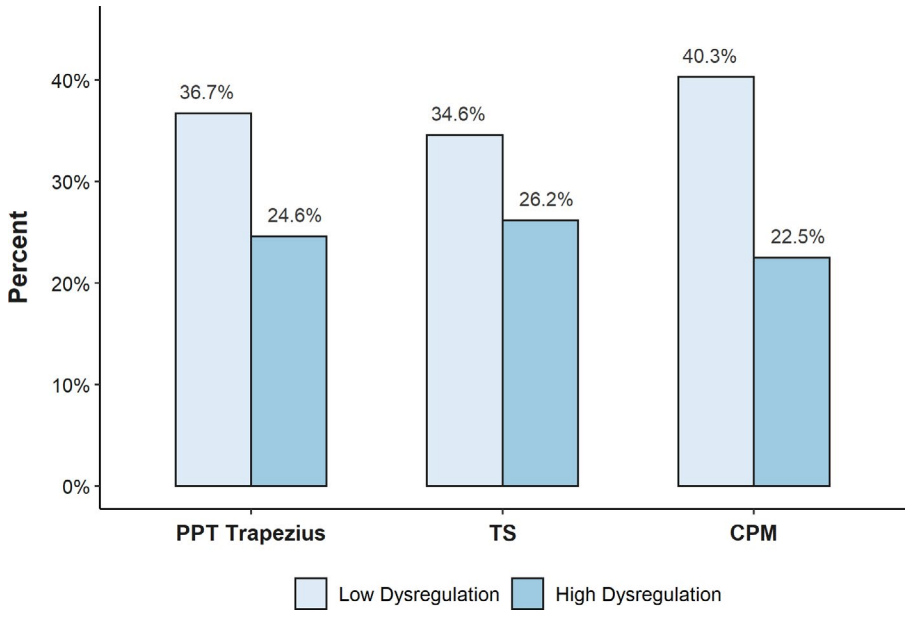


**Figure 1.** Percentage of participants in each quantitative sensory testing measures group who achieved a good response to disease-modifying antirheumatic drug treatment according to the European League Against Rheumatism response criteria. Patients were classified as having low dysregulation or high dysregulation according to pain pressure threshold (PPT) at the trapezius muscle, temporal summation (TS), and conditioned pain modulation (CPM).

**Table 2.** ORs for achieving good EULAR response in participants with high PPT, temporal summation, and CPM dysregulation*

| QST measure | Unadjusted OR (95% CI) | Adjusted OR (95% CI)† |
|---|---|---|
| High PPT dysregulation | 0.56 (0.29–1.10) | 0.59 (0.28–1.23) |
| High temporal summation dysregulation | 0.67 (0.33–1.34) | 0.60 (0.27–1.34) |
| High CPM dysregulation | 0.43 (0.22–0.83)‡ | 0.40 (0.19–0.83)‡ |

* ORs = odds ratios; EULAR = European League Against Rheumatism; PPT = pressure pain threshold; CPM = conditioned pain modulation; QST = quantitative sensory testing; 95% CI = 95% confidence interval.
† Adjusted for age, sex, race, body mass index, education level, seropositivity, rheumatoid arthritis disease duration, Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance, PROMIS depression, and modified Charlson comorbidity score.
‡ $P < 0.05$.

the high CPM dysregulation group versus the low CPM dysregulation group in an exploratory analysis. The mean ± SD decrease in TJC was 3.52 ± 6.14 among those with high CPM dysregulation and 6.29 ± 7.25 among those with low CPM dysregulation (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41440/abstract).

In a secondary analysis, we assessed the percentage of participants who achieved good EULAR response with different combinations of dysregulation in pain facilitation (temporal summation) and pain inhibition (CPM). The percentage of participants who achieved a good EULAR response in each category was: 52.6% with low temporal summation and low CPM dysregulation, 34.9% with predominant temporal summation dysregulation, 24.2% with predominant CPM dysregulation, and 21.8% with high temporal summation and high CPM dysregulation (Figure 2). The adjusted OR for achieving good EULAR response decreased with an increasing number of central dysregulation categories ($P$ for trend = 0.007) (Table 3). When each category was compared to the referent (low temporal summation and low CPM dysregulation), the only statistically significant association was between the group with both temporal summation and CPM dysregulation and a good EULAR response (OR 0.23 [95% CI 0.07–0.73]).

## DISCUSSION

The objective of this longitudinal prospective study was to assess pain centralization as a predictor of response to DMARD therapy in participants with active RA. In the adjusted analysis, high CPM dysregulation (alone and in combination with high temporal summation dysregulation) was identified as a significant predictor of lower odds of achieving a good EULAR response. These results suggest that pain centralization may play a role in DMARD response in patients with active RA. The specific mechanisms of this finding may include inefficient descending endogenous analgesia, of which low CPM is a surrogate marker (24,27).

To our knowledge, this study is the first to report that inefficient CPM is associated with lower odds of treatment response in patients with a systemic inflammatory condition, such as RA. Similar observations have been reported in noninflammatory pain conditions, such as OA. For example, in a study of 42 patients with knee OA, less efficient CPM was associated with less pain improvement in response to treatment with ibuprofen and

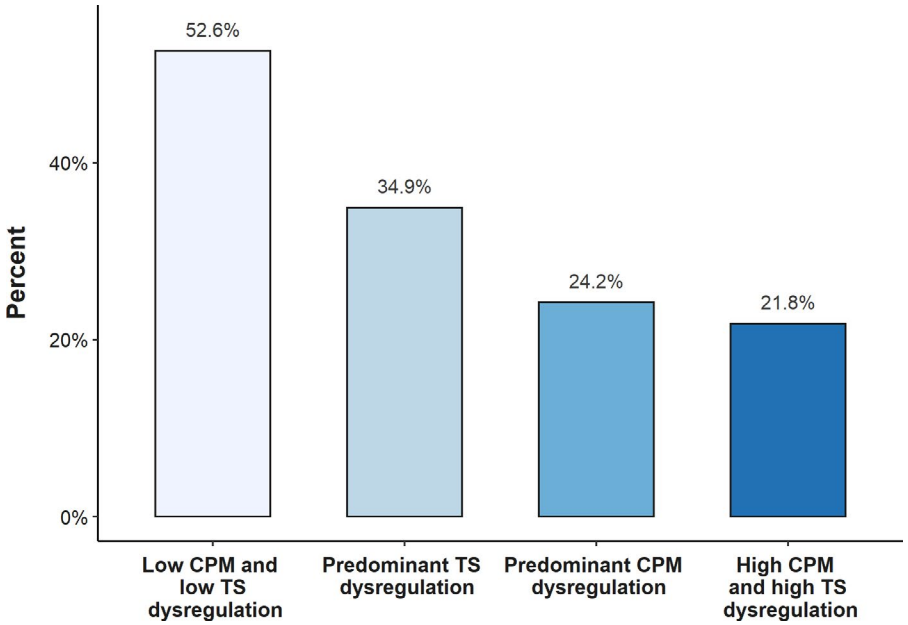


**Figure 2.** Percentage of participants in each temporal summation (TS) and conditioned pain modulation (CPM) dysregulation group who achieved a good response to disease-modifying antirheumatic drug treatment according to the European League Against Rheumatism response criteria. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41440/abstract.

**Table 3.** ORs for achieving good EULAR response by temporal summation and CPM central dysregulation group*

| | Unadjusted OR (95% CI) | Adjusted OR (95% CI)† |
|---|---|---|
| Low temporal summation and low CPM dysregulation | 1.00 (referent) | 1.00 (referent) |
| Predominantly temporal summation dysregulation | 0.48 (0.16–1.45) | 0.49 (0.14–1.67) |
| Predominantly CPM dysregulation | 0.29 (0.09–0.96)‡ | 0.31 (0.08–1.13) |
| High temporal summation and high CPM dysregulation | 0.25 (0.09–0.71)‡ | 0.23 (0.07–0.73)‡ |
| *P* for trend | 0.0072 | 0.0077 |

* ORs = odds ratios; EULAR = European League Against Rheumatism; CPM = conditioned pain modulation; 95% CI = 95% confidence interval.
† Adjusted for age, sex, race, body mass index, education level, seropositivity, rheumatoid arthritis disease duration, Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance, PROMIS depression, and modified Charlson comorbidity score.
‡ $P < 0.05$.

acetaminophen (28). Similarly, in a study of 35 patients with knee OA, inefficient CPM predicted decreased response to diclofenac gel (29), and in a study of 14 patients with knee OA, inefficient CPM before total knee arthroplasty (TKA) predicted less improvement in pain 6 months after TKA (30).

The observation that CPM in response to an experimental stimulus predicts decreased response to peripherally directed treatments may be explained in multiple ways. One explanation is that impairments in inhibitory pain processing are uncoupled from peripheral nociceptive input, resulting in continued pain despite resolution of peripheral nociceptive input. An alternative explanation is that patients with low baseline CPM have already fully activated their inhibitory pain pathways due to existing pain from their clinical condition(s) and are thus unable to mount an additional inhibitory response to the experimental stimulus. Both explanations are consistent with the results of our exploratory analysis, which indicate that the association between low CPM and poor DMARD response likely reflects less improvement in pain sensitization (measured by TJC), as opposed to less improvement in inflammation (measured by SJC and CRP level).

In contrast, we did not observe a statistically significant association between PPTs and a good EULAR response. In other painful conditions, the relationship between PPTs and treatment response has been conflicting (31). Wylde et al reported that low preoperative PPTs were associated with persistent pain following TKA (32). However, the magnitude of this finding was small, and other studies failed to find a relationship between PPTs and pain following joint replacement (33). It is possible that we did not see a statistically significant relationship between PPTs and treatment response because PPTs reflect overall dysregulation of pain processing, which could be the result of a mixture of altered mechanisms, including both inefficient pain inhibition and enhanced pain facilitation.

Similarly, we did not see a statistically significant association between temporal summation and EULAR response. Consistent with our findings, Christensen et al did not find a statistically significant association between temporal summation and change in DAS28 at 4 months following DMARD initiation (34), and the association between temporal summation and treatment response has been inconsistent in studies of other musculoskeletal conditions. In a systematic review by Georgopoulos et al, pooled data from 4 studies indicated that temporal summation predicted pain in musculoskeletal conditions with an unadjusted correlation coefficient of 0.37, but the association was not statistically significant in adjusted analyses (35). In contrast, a subsequent study reported that preoperative facilitated temporal summation was associated with pain following TKA in analyses adjusted for Kellgren/Lawrence scale, warm detection threshold, and heat pain threshold (36).

A potential explanation for the differences in results seen across QST modalities may be that suppression of peripheral inflammation affects specific mechanisms of central pain processing differently. For instance, temporal summation has been hypothesized to be a bottom-up process, which arises from ongoing noxious peripheral stimuli (26,37). If an ongoing noxious peripheral stimulus is required to maintain pain centralization, we would expect resolution of pain following treatment of inflammation. Thus, we would not expect an association between temporal summation and treatment response. In contrast, descending inhibition (CPM) may not resolve following resolution of noxious input, making baseline dysregulated CPM a more likely predictor of poor DMARD response. Therefore, some QST modalities may be associated with poor treatment response, while others are not. It is also possible that the association between specific QST modalities and treatment response differs depending on the duration of the initial peripheral noxious stimulus. For example, the effects of heightened temporal summation may be reversible if the duration of the initial noxious peripheral stimulus is limited but become irreversible with time. Future studies are needed to further elucidate the role of temporal summation and CPM in the development and maintenance of chronic pain.

These results have important clinical implications. These findings indicate a role for pain centralization in DMARD response in RA. For a subgroup of patients, remission, as defined by composite disease activity markers, may not be possible to achieve without addressing pain centralization. Furthermore, pain centralization may involve multiple pathways such as the ascending pain pathways, as indicated by temporal summation, and the descending endogenous analgesia pathway, as indicated by CPM. Here, we provide evidence for inefficient endogenous analgesia as a mechanism of pain centralization leading to inadequate EULAR response in RA. Clinicians should consider therapy targeting this pathway, such as serotonin norepinephrine reuptake

inhibitors (SNRIs). For instance, Yarnitsky et al reported that inefficient CPM predicted a good response to the SNRI duloxetine in patients with painful diabetic neuropathy (38). In contrast, in a previous study, our group did not observe any differences in pain scores between RA patients treated with the SNRI milnacipran versus those treated with placebo (39). However, those patients were not stratified by CPM levels. Future studies examining the use of SNRIs in RA patients with and those without efficient CPM would be useful in determining whether CPM may be utilized to identify individuals who are likely to respond to an SNRI as an adjunctive treatment for pain in RA.

Our study has several strengths. CPIRA is the largest cohort with comprehensive QST data in RA, including PPTs, temporal summation, and CPM. Our QST protocols were adapted from protocols commonly used in the literature, enabling comparison across previous studies. The use of temporal summation and CPM in addition to PPTs allowed for interrogation of specific mechanisms of pain centralization. Additionally, our study was comprehensive in the collection of clinical variables which enabled us to account for important potential confounders, such as depression, sleep disturbance, and medical comorbidities.

This study also has a few important limitations. First, there was missing data. However, comparing the demographic data from the included and excluded patients revealed no meaningful differences. Second, interpretation of QST categories as dysregulated may be limited, as we did not include a control group of healthy individuals for comparison. Third, while DAS28-CRP response contains an objective marker (CRP level), we did not use more sensitive methods of detecting synovitis such as ultrasound or magnetic resonance imaging (MRI). Fourth, the measurement properties of current CPM paradigms are imperfect, as evidenced by the lower ICC compared to other QST measures, and it is certainly possible that the chosen method of analysis may influence results. Future studies may focus on finding improved methods of studying descending modulation of pain. For instance, better results may be achieved using imaging of the descending pathways, such as functional MRI or MR spectroscopy. Lastly, given that this was not a randomized, controlled trial, confounding by unmeasured factors may have impacted the observed relationships.

In summary, this study provides evidence that pain centralization is associated with inadequate EULAR response. Specifically, we report a potential role for the endogenous descending analgesic pathways, reflected by inefficient CPM in response to a noxious stimulus, in poor treatment response in patients with RA. Clinicians should consider pain centralization as a possible reason for the perception of persistent disease activity in RA. Patients with abnormalities in their CNS pain processing pathways may be candidates for treatment with cognitive behavioral therapy or centrally acting agents. Recognition of pain centralization as a contributor to disease presentation could facilitate optimizing a patient's medication regimen without escalating DMARD therapy, which is accompanied by inherent risks.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Heisler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data.** Song, Wohlfahrt, Marder, Bolster, Bingham, Dunlop, Neogi, Lee.

**Analysis and interpretation of data.** Heisler, Song, Muhammad, Clauw, Dunlop, Neogi, Lee.

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